Remarks

Rejection under 35 U.S.C. §112, First Paragraph (New Matter)

Claims 60 and 67 were rejected under 35 U.S.C. §112, first paragraph, as being considered to contain matter that was not described in the specification. The Office Action states, on page 3, first full paragraph, that "both SEQ ID NO: 15 and 16 contain polyHis tag on the C-terminal, wherein the specification fails to provide support for the amino acid 58 through the C-terminus of either SEQ ID NO: 15 or 16 which encompass the polyHis tag".

Applicants respectfully traverse these grounds for rejection. Applicants wish to draw attention to the specification on page 17, lines 14-17, where it states:

> SEQ ID Nos: 15 and 16 are the amino acid sequences of the extracellular domains of nectin-3α and nectin-3β, respectively, fused at their C termini to a FLAG® peptide sequence (amino acids 405 through 420 of SEQ ID NO:15 and amino acids 366 through 381 of SEQ ID NO:16) and a C-terminal polyHis stretch of six histidine residues.

Applicants' invention provides both full length and mature forms of nectin-3α and β, see page 14, lines 27-31, where the mature form of nectin-3α is from amino acid residue x_1 to amino acid residue 549 and nectin-3β is from amino acid residue x_1 to amino acid residue 510, wherein x_1 is an amino acid between and including residues 51 to 58. The extracellular domain of nectin-3α extends to amino acid 404 of SEQ ID NO:6 and the extracellular domain of nectin-3β extends to amino acid residue 365 of SEQ ID NO: 12, see page 5, lines 18-24.

Withdrawal of the rejection of claims 60 and 67 under 35 U.S.C. §112, first paragraph (new matter), is respectfully requested.

Rejection under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 59-111 stand rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement.

With regard to claims 59-78, the Office Action states, on page 4, last full paragraph, that the claims recite the term "comprising" which is open-ended and expands the claimed

sequences to include additional non disclosed amino acids on either of both sides of the N- and C- terminal of the polypeptide. The Office Action alleges that the specification fails to provide sufficient guidance as to which amino acids outside the claimed core amino acids are essential for maintaining nectin 1 binding activity and same function.

Applicants respectfully traverse these grounds for rejection. "Comprising" is a term of art used in claim language, which means that the named elements are essential, but that other elements may be added and still form a construct within the scope of the claims. *In re Baxter* 656 F. 2d at 686, 210 USPQ at 802. Polypeptides within the scope of claims 57-78 comprise a functional domain of nectin-3α. The claimed polypeptides require the presence of amino acid residues 58 through 404 of SEQ ID Nos: 4 or 6. Applicants have fulfilled the requirements for enablement by teaching throughout the specification how to make and use polypeptides comprising this "essential element" that would fall within the scope of the claimed invention. The Applicants also teach how to make embodiments that would fall within the scope of the claimed in invention. These include, but are not limited to, N- or C-terminal fusions (see page 8 and Examples 3 and 4 for the tagged Extracellular domain used in the assays), fusions joined by peptide linkages (see page 19) fusions derived from immunoglublins such as Fc (see page 18) and other embodiments which were known in the art at the time of filing the present application. Example 4 teaches that a soluble nectin-3FC fusion protein comprising amino acid residues 58-404 of SEQ ID NO: 6 binds strongly to nectin 1 transfected cells.

Applicants also submit that it is not necessary to recite every possible embodiment in order to fulfill the requirements of enablement. In *Atlas Powder Co. v. E.E. Du Pont De Nemours*, 750 F.2d 1560 (1984) at page 1576, the court addresses the enablement requirements. The court upheld the district court's decision that it would have been impossible for the patent at issue to list all possible operative embodiments, and that even if some of the claimed embodiments were inoperative, the claims were not necessarily invalid (at page 1576), since one of skill in the art would know how to find operative embodiments based on the disclosure.

Applicants maintain that the instant application provides sufficient teachings to allow one of skill to make and use the embodiments encompassed by the scope of the claims.

With regard to claims 79-111, the Action asserts that "Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein that are

tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions". The Action also provides that due to large quantity of experimentation necessary to obtain "85%, 90%, 95% or 99% nectin-3 polypeptide variants, to generate the infinite number of derivatives recited in the claims...undue experimentation would be required. Making and testing such polypeptides is clearly well outside realm of routine experimentation." Emphasis added.

Applicants respectively traverse these grounds for rejection. As to the issue of undue experimentation and quantity of experimentation, MPEP 2164.06 provides that:

> "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

MPEP 2164.06 also provides:

> "In the chemical arts, the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identity a compound within the scope of a claim, then this great quantity of experimentation should be considered in the overall analysis. Time and difficulty of experiments are not determinative if they are merely routine".

The Action provides no evidence that the speculated experimentation, if even necessary, would be beyond that which is routine to one of skill in the art. The specification teaches a multitude of methods used in the art to make and use the sequences of the claimed invention. For example, percent identity can be determined either visually or mathematically. Various art recognized computer programs and algorithms as well as a table of percent identities for human nectins that were generated using such algorithms are provided, see page 16, first paragraph. Many of these tools are readily available via the Internet and are known and used by those skilled in the art.

Methods for the production of polypeptides, via recombinant expression or known conventional chemical synthesis, which are known and practiced in the art are described, for example, at page 22, last paragraph.

Numerous assays for identifying and characterizing the function of the claimed sequences are known in the art and are provided on pages 36-40. Assays related to endothelial cell migration are exemplified in the specification, in particular in the paragraph bridging pages 36 and 37 Assays to Identify Modulators of Intracellular Communication, Cell Adhesion or Migration or Immune Activity". Working examples are also found in Examples 4 and 5 of the specification. Example 4 provides for binding of nectin-3 to human endothelial cells and Example 5 provides modulation of endothelial cell migration by nectin-3. Example 6, endothelial cell migration is measured as a rate of closure of circular wounds.

Applicants wish to direct particular attention to pages 6-10 and Tables 2 and 3, where the identification of positions in the protein that are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions, are disclosed. The specification teaches that amino acid substitutions and other alterations (deletions, insertions and the like) to conserved residues are predicted to more likely to alter or disrupt nectin polypeptide activities, see for example the paragraph bridging pages 6 and 7. Tables 2 and 3 provide alignments of known nectin polypeptide sequences and highlight conserved regions and amino acid residues. The specification also teaches that substitutions or alterations to those positions illustrated in the nectin polypeptide sequence alignments that are not conserved are less likely to affect the function of the altered nectin polypeptide. An example of substituted sequence is provided on page 6 at lines 32-33, where substitution of a lysine or chemically similar histidine for arginine at consensus position 98 (from alignment provided in Table 2) is less likely to alter function of the polypeptide than would the substitution of tryptophan or tyrosine. Substitution of Pro for Leu at residue 5 and Gly for Arg at residue 6 of the nectin 3α and β polypeptides were functional for several sequences containing this alteration, see the top of page 7. On page 8 is provided a variant lacking the first Ig domain typical of a nectin protein. This form would not bind to nectin-1 but would be capable of forming homodimers with other nectin-4 forms and would bind afadin.

Applicants have taught one of skill in the art how to make and use the claimed polypeptides using methods and materials either known and used in the art or provided by Applicants in their application. Any experimentation would therefore be merely routine.

With regard to Skolnick and Fetrow, Metzler et al. and Martinez et al., the Action has not addressed the issues raised by Applicants that when each reference is read as a whole that none of the cited references can be considered to teach an inability of the skilled artisan to predict the functionality of nectin polypeptide variants from their amino acid sequence, especially when nectin-3 function has already been experimentally established.

The Action also asserts that based in these references it is only through excessive and undue experimentation can confirm the artisan's best guess as to the function of the structural related protein can be confirmed and that that Applicants provide little or no guidance to enable one of skill in the art to determine, without experimentation, the positions that are tolerant to change and the nature and extend of changes.

As discussed in detail above, a considerable amount of routine experimentation is permissible and the inclusion of inoperable embodiments may not invalidate a claim. The Action has not put forth any evidence that the speculated experimentation, if even necessary, would be anything but routine for one of skill in the art.

Applicants respectfully submit that for at least the reasons stated above, the rejection of claims 59-111 under 35 U.S.C. §112, first paragraph (enablement), has been traversed and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 59-111 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the invention.

The Action states the specification does not identify variants and does not disclose a representative number of members. No variants were made or shown to have activity. Only the polypeptides of nectin-3 α, β and γ are disclosed. The Action alleges that the Applicants' specification provides only an invitation to experiment by trial and error.

Applicants respectfully traverse these grounds for rejection. As described above and in the previous responses, the specification describes the claimed polypeptides and their functional properties in sufficient detail as to convey to one of skill in the art that Applicants were in possession of the invention at the time of filing. As discussed in detail above, the specification, particularly the Example section, describes the construction various

polypeptides and the identification and characterization of some functional characteristics of those polypeptides, including the ability to inhibit endothelial cell migration.

Applicants submit that under the Examination Guidelines set forth by the US PTO, the written description requirement for a claimed genus may be satisfied by the description of a representative number of species or the disclosure of relevant identifying characteristics, sufficient to show the Applicants were in possession of the claimed genus. Guidelines for Examination of Patent Applications under 35 U.S.C. §112, First Paragraph (Written Description) Requirement, 66 Fed. Reg. 1099, at 1106:

> "An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics...If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met." Emphasis added

Applicants submit that the Guidelines clearly provide that acceptable identifying characteristics include both sequences and functional characteristics. Among the functional characteristics of the claimed polypeptides are inhibition of endothelial cell migration and nectin-1 binding. The examples provided in the Guidelines are sufficiently detailed, relevant identifying characteristics that provide evidence that the Applicants were in possession of the claimed invention include, "complete or partial structure...functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of these characteristics." Applicants also submit they have disclosed sufficient identifying characteristics to meet the written description requirements for the claimed polypeptides requiring amino acid residues 58 through 404 of SEQ ID Nos: 4 or 6 and polypeptides that share at least 80% amino acid identity across the length of amino acid residues 58 through 404 of SEQ ID NOs:4 or 6, since Applicants provide a reference sequence, percent identity limitations and the functional limitation of inhibiting endothelial cell migration. Applicants submit that the identified sequences and functional characteristics of the claimed polypeptides clearly demonstrate that Applicants were in possession of the

claimed polypeptides. Applicants also submit that the characteristic of a polypeptide comprising amino acid residues 58 through 404 of SEQ ID Nos: 4 or 6 or polypeptides that share at least 80% amino acid identity across the length of amino acid residues 58 through 404 of SEQ ID Nos: 4 or 6 is undeniably a partial structure, which is acknowledged in the Guidelines as being a sufficient, relevant identifying characteristic. These structural characteristics, particularly when coupled with the functional characteristic of inhibiting endothelial cell migration, clearly establish that Applicants were in possession of the claimed invention.

Applicants submit that the disclosure in the specification of the sequences, the requirements of having at least 80% identity and the ability to inhibit endothelial cell migration, effectively describes a representative number of species, so as to satisfy the written description requirement. The genus of polypeptides falling within the scope of the claimed invention includes a limited number of species. Applicants note that the Guidelines explicitly state that:

> "[a] 'representative number of species' means that the species which are adequately described are representative of the entire genus" and that "there may be situations where one species adequately supports a genus." *Id.* At 1106.

The Guidelines further note that:

> "satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by members of the genus in view of the species disclosed"

and that

> "[d]escription of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." Id.

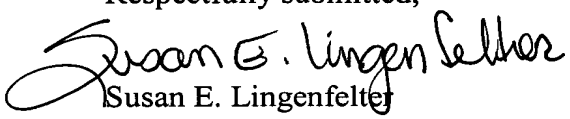
Applicants submit that the skilled artisan would clearly recognize that Applicants were in possession of the claimed genus based upon the disclosure of the polypeptides.

Applicants respectfully submit that for at least the reasons stated above, the rejection of claims 59-111 under 35 U.S.C. §112, first paragraph (written description), has been traversed and withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicants submit that the presented claims are in condition for allowance. A favorable action is earnestly requested. Applicants' attorney invites the Examiner to call her at the number below if any issue remains outstanding.

Respectfully submitted,



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Filing Date:	October 5, 2001	Examiner:	Maher M. Haddad

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